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NIAID STRATEGIC PLAN

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DRAFT

TABLE OF CONTENTS

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DIRECTOR'S FOREWORD

The National Institute of Allergy and Infectious Diseases (NIAID) is the component of the National Institutes of Health (NIH) which is charged with the responsibility to support research on immunological and infectious diseases. The NIAID has grown significantly over the last fifteen years, largely due to three factors. The first is the emergence of HIV/AIDS in the early 1980s, which shattered the prevailing concept that the era of infectious diseases was drawing to an end due to the remarkable successes brought about by new vaccines and new therapies. Second, the Institute has historically placed basic research in immunology and microbiology as one of its highest priorities for support. This commitment is now paying major dividends with remarkable new insights into the immune system and the human response to infection, the physiology and genetics of microbes that cause infectious diseases, and the pathogenesis of infectious disease processes. All of these contributions in basic research provide new approaches to the clinical and public health problems that are at the heart of the Institute's mission. Finally, it is now clear that infectious diseases continue to emerge unpredictably, and sometimes explosively, around the world. The modern miracles of transportation can rapidly transform a new infectious disease problem into a global problem. The last decade alone has been witness to many new problems such as the resurgence of cholera in the Americas (for the first time in over a century), the emergence of Hantavirus in the continental United States, new influenza viruses, and many other threats. In addition, the world now faces the menace of bioterrorism. These are only some of the problems that will remain challenges for the immunology and microbiology research communities.

The NIAID is facing these challenges at a time when the technological opportunities have never been greater. The rapid pace of scientific progress in immunology and microbiology opens many opportunities for progress. In addition, a surge of new technologies now makes tasks, such as genome sequencing, which were daunting a decade ago, almost routine. The simple fact is that the Institute now faces the challenge of many more choices for investment in research than it did even five years ago. The rapidity of change and the expansion of possible choices for directions in research make planning a more critical element of the Institute's day-to-day operation. The need to set priorities among the opportunities for advances is the primary motivation driving the development of an NIAID strategic plan.

The second motivation for NIAID the strategic plan stems from the 1998 Institute of Medicine Report, *Scientific Opportunities and Public Health Needs: Improving Priority Setting at the National Institutes of Health*, which recommended that the NIH Director receive a strategic plan from each Institute and Center (IC). To address this recommendation, the Office of the Director of NIH asked each IC to develop, with public input, a forward-looking strategic plan with members of Congress and the public as its primary audience.

The plan described in the following document is an effort to establish some clear priorities for action by the NIAID in the next three to five years. As a capstone for previous planning efforts, the Strategic Plan describes broad-based Institute priorities that will serve as a touchstone as the Institute develops future programs, policies, and initiatives. However, it should also be clear that two major factors will affect this plan over time. The first of these is that there are natural and logical areas of overlap in the four areas covered by this plan. This is an advantage in our view since it reinforces the clear trend in science towards multidisciplinary research. Second, it is difficult to predict with certainty the magnitude of change we will experience in the next three to five years. These factors and others will certainly cause us to reexamine this plan over time. But it is intended to be a dynamic document that identifies areas of priority in broad-brush strokes precisely because the plan itself must be flexible.

INTRODUCTION

The NIAID Mission Statement

The NIAID conducts and supports research that strives to understand, treat, and ultimately prevent the myriad infectious, immunologic, and allergic diseases that threaten millions of human lives.

NIAID's stewardship of this mission is driven by two convictions. The first conviction is that a strong research base is of paramount importance in being prepared to address future threats of unknown character. The breadth and depth of our understanding of immunology and microbiology was central to our ability to rapidly develop powerful treatments for AIDS. Sustaining a strong research base in immunology and microbiology will be key to stopping the next global threat. It is also critical to making continual progress across the broad front of existing and as yet unconquered infectious and immune-mediated diseases. Although space limitations prevent the strategic plan from explicitly discussing every disease of concern to NIAID, the Institute is resolved to conduct and support research to understand, treat, and prevent the full range of infectious and immunologic diseases, including sexually transmitted diseases (STDs), fungal infections, food-borne illnesses, chronic fatigue syndrome (CFS), and primary immunodeficiency diseases.

The second conviction is that the fields of immunology, microbiology, and infectious disease are related and complementary. Thus, while the framework for the strategic plan has four cornerstones -- immune mediated diseases and immune tolerance, AIDS, emerging infectious diseases, and vaccines -- considerable synergy exists within that framework

The parameters of NIAID's mission are defined on one hand by scientific opportunity and on the other by public health need.

SCIENTIFIC OPPORTUNITY

Years of investment in basic research have generated remarkable possibilities to address immune-mediated and infectious diseases. Among just a few of the most exciting scientific opportunities are:

- Induction of immunologic tolerance could be used to treat many immune-mediated diseases and to achieve long-term, durable graft survival, a major barrier to successful transplantation.
- Advances in the understanding of the genetic basis of asthma and allergy provide new opportunities for prevention and treatment of those diseases.
- Knowledge of genetic organization, in combination with expanded knowledge of the molecular and immunologic interplay between host and pathogen, provides the basis for renewed efforts to develop vaccines for malaria and tuberculosis.
- Combined with technological advances such as consensus PCR, emerging human genome sequence information provides new opportunities to identify infectious causes of chronic disease -- discoveries that will revolutionize clinical diagnosis and treatment of these debilitating conditions.

It is clear that the research opportunities far surpass the resources available. Therefore, it will be necessary to focus our research efforts on those areas where the scientific opportunities are the most promising and the need is the greatest. This plan attempts to do this by focusing on four broad cornerstone areas: immune-mediated diseases, HIV/AIDS, emerging infectious diseases and vaccine research.

PUBLIC HEALTH NEED

The Impact of Infectious Diseases

Infectious diseases are the second largest cause of death worldwide. In the United States they are the third largest cause of death and cost the nation approximately $125 billion annually.

- Tuberculosis (TB) - TB is responsible for more deaths worldwide than any other single infectious disease. Almost two billion people are infected worldwide. Of those with healthy immune systems, approximately 10% will develop active TB disease and be able to spread the organism to others. Moreover, drug resistant TB is widespread, having been found in every country surveyed for its presence.
- Acquired Immunodeficiency Disease (AIDS) - In the United States, an estimated 650,000 to 900,000 people are living with HIV and the rate of new HIV infections, approximately 40,000 per year, continues at an unacceptably high level. Half of newly infected individuals are people younger than 25 who were infected sexually and the HIV virus continues to affect minority populations disproportionately. Although new AIDS diagnoses and deaths have fallen significantly during the past three years in developed countries, the next generation of therapies remains a priority. That is because many HIV-infected individuals have not responded adequately to current medications, cannot

tolerate their toxicities, or have difficulty complying with treatment regimens that involve extremely complicated and demanding dosing schedules. Even in patients who are successfully treated and have extremely low bloodstream levels of HIV, the virus persists. Moreover, the emergence of HIV strains resistant to current drugs is a growing problem. In the developing world, the HIV/AIDS epidemic continues to accelerate. In 1998, HIV/AIDS was the fourth leading cause of mortality worldwide, resulting in an estimated 2.3 million deaths. Beyond the human tragedy of HIV/AIDS, the economic costs of the epidemic pose a significant impediment to the economic growth and political stability of many countries. In developing countries and in segments of the U.S. population, anti-HIV therapies are frequently beyond financial reach. Accordingly, effective, low-cost tools of HIV prevention, such as a vaccine, are needed urgently to bringing the HIV epidemic under control.

- Malaria - Malaria has been undergoing a resurgence in recent years and 500 million cases occur each year in the world, with a death toll estimated at 2.7 million. Initial success in controlling malaria has been reversed due to increased resistance of the parasite to drugs, changing epidemiological and ecological patterns, increased resistance of mosquitoes to standard insecticides, and lack of sustainability of existing control measures.
- Influenza - At least five major influenza pandemics have occurred since 1889, the worst of which, the pandemic of 1918-1919, caused more deaths than World War I. Since 1918, at least three pandemics have occurred. In the U.S., 20-26% of the population is estimated to have a yearly influenza-associated illness and nationwide an annual average of 20,000 deaths and 130,000 to 170,000 hospitalizations are associated with influenza. The economic burden of an influenza epidemic can be staggering; total calculated costs of this disease have been estimated at $4.6 billion/year.
- Hepatitis - Hepatitis (liver inflammation) can be caused by a variety of viruses. The most common include the following:
  - Hepatitis A causes acute liver inflammation and is generally transmitted from contaminated food or water. In 1997, almost 28,000 cases of HAV were reported in the United States. HAV leads to few deaths in the U.S., where it is the primary cause of hepatitis. However, this virus can be deadly in developing countries.
  - Hepatitis B is an easily transmitted, blood borne disease that leads to chronic infections, especially in neonates infected at birth. Chronic HBV infection is a leading cause of liver cancer. In 1997, almost 9,000 cases of HBV were reported to the CDC. Worldwide, approximately 1 million chronic HBV carriers die of liver cancer or cirrhosis during adulthood.
  - Hepatitis C virus (HCV) also is blood borne. Almost 4 million people in the U.S. have been infected with HCV and 2.7 million are chronically infected. HCV may not cause symptoms for 20 to 30 years, yet during that time the infection is damaging the liver. About 70% of infected individuals eventually develop chronic liver disease, 15% develop cirrhosis, and 5% die. Because HCV is asymptomatic for a long time, many infected individuals are not aware that they are carriers and unknowingly transmit the disease to others. Better diagnostics have driven incidence down from 180,000 in 1984 to about 3,000 in 1997. To date however, a good vaccine candidate has not been identified.

- Emerging Infections - There are numerous emerging infectious agents among the viruses, bacteria, protozoa and fungi that make up the microbial world.
  - Among viruses, the Hepatitis C virus and Hantavirus are the best known newly emergent infectious threats in the U.S. Worldwide, however, dengue kills 5,000 children a year, fatal cases of monkeypox are reported from the Congo, and in 1997 evidence of a new paramyxovirus that can cause symptoms in humans was isolated from pigs.
  - The bacterial killer tuberculosis is classed as an emerging disease because multidrug-resistant strains are evolving. Other emerging bacterial infections that can be fatal include *Vibrio cholerae*, multidrug resistant salmonella, and *Staphylococcus aureus*.
  - The malaria parasite is reappearing due to development of antimicrobial resistance. Other emerging parasitic diseases include *Cryptosporidium parvum*, *Cyclospora cayetanensis*, Chagas' disease, onchocerciasis, and neurocysticercosis.

  Because the frequency of world travel makes the United States part of a global community, diseases that emerge in foreign countries are also health threats in the U.S.
- Bioterrorism – Increasing concerns about possible biological terrorist attacks against the U.S. have surfaced. Terrorist incidents involving biological agents are uniquely complicated because of the large number of potential agents, their long incubation periods and delayed onset of disease, and their potential for secondary spread. In addition to naturally occurring pathogens, agents used by bioterrorists may be genetically engineered to resist current therapies and evade vaccine-induced immunity. Biological agents most likely to be used in a bioterrorist attack are anthrax, plague, smallpox, and tularemia.

The Impact of Immunologic Diseases

Immunologic diseases -- asthma and allergy, primary immunodeficiencies, and autoimmune diseases -- afflict millions of Americans and result in considerable mortality, morbidity, and medical costs. Also, transplant rejection, while not a malfunction of the immune system, is a problematic response that remains a challenge.

- Allergic Diseases and Asthma - Allergies and asthma are major causes of illness and disability in the United States. More than 50 million Americans (1 out of every 5) suffer from allergies and/or asthma. Asthma is on the increase among U.S. children and places a disproportionate burden on disadvantaged inner-city populations. Allergic diseases include allergic rhinitis, asthma, atopic dermatitis, urticaria and anaphylaxis. Anaphylaxis, the most severe form of allergic reaction, is a life-threatening reaction associated with cardiovascular collapse.
  - There are 9.2 million outpatient visits per year for allergic rhinitis.
  - Chronic sinusitis is the most commonly reported chronic diseases, with 14.7% of the population (about 38 million persons) affected.
  - Allergies to food, insect venom, and drugs can be severe, even fatal.
  - In 1994, there were 14.6 million persons (5.6%) in the United States reported to have asthma, and asthma was the first-listed diagnosis for more than 451,000

hospitalizations. Although asthma is a disease with low mortality, its economic costs are enormous with an estimated cost in the United States in 1990 of $6.2 billion.

- Autoimmune Diseases - Autoimmune diseases are illnesses in which the immune system attacks the body's own tissues. Examples include diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis. While many autoimmune diseases are rare, collectively these diseases afflict more than 5% of the U.S. population and a disproportionate number of women. The chronic nature of the diseases leads to high medical costs.
  - Insulin Dependent Diabetes Mellitus - Also called type I diabetes, this disease is caused by immune destruction of the pancreatic cells responsible for the production of insulin. The resulting lack of insulin contributes to long-term complications affecting the kidneys, eyes, nerves, heart and feet of diabetic patients. This diseases afflicts an estimated 300,000-500,000 Americans, 123,000 of whom are under 20 years of age. The total costs for medical care, disability, work loss, and premature mortality are estimated to range between $4.6 and $9.2 billion annually.
  - Systemic Lupus Erythematosus (SLE) - At least 239,000 Americans are diagnosed with or suspected of having SLE, a disease that predominately affects women (greater than 90 percent of the cases) and is more common and more severe in African American women. SLE damages multiple tissues and organs. Muscles, skin, joints, kidney as well as the brain and nerves may be affected.
  - Rheumatoid Arthritis (RA) - RA afflicts an estimated 2.1 million Americans or about 1% of the population. It results in 25,000 hospitalizations per year, 2.1 million lost work days annually, and 12 physician visits per patient per year. RA usually begins as pain, swelling and tenderness of the small joints of the hands and feet. The mechanisms that trigger the inflammatory process that may cause destruction and deformity of the affected joints are not completely understood
  - Multiple Sclerosis (MS) - MS, a chronic, inflammatory disease of the central nervous system, is the second most likely condition to cause more than 30% limitation in physical and outdoor activities. The disease, which frequently results in permanent disability, afflicts an estimated 250-350,000 Americans.
- Graft Rejection - For many victims of kidney failure, diabetes, leukemia, heart and liver disease, the ultimate treatment must be transplantation of an organ or tissue. Yet, often transplants fail. Graft rejection is second only to organ shortage as an impediment to long-term transplantation success.

ACCOMPLISHMENTS

The contributions of NIAID-supported investigators have been outstanding and extend from basic discoveries in microbiology and immunology to the development of vaccines, drugs and diagnostics.

Immune Mediated Diseases

Decades of investment by NIAID in research on the immune system -- on immune activation and regulation and on the genetic basis of disease susceptibility -- have yielded advances in diagnosis, treatment, and prevention as well as a level of conceptual understanding that positions the field for highly significant clinical breakthroughs.

Basic research in immunology:

- Discovered mechanisms of antibody diversity
- Defined two types of immunity: humoral and cell-mediated
- Defined role of thymus in immunologic processes (the role of the thymus in T-cell selection)
- Discovered immune response genes
- Discovered the genetic bases of many primary immunodeficiency disorders
- Discovered, at the molecular level, how the immune system mounts a response to a specific challenge
  - Description of molecular structure of immunoglobulins
  - Delineation of role of MHC in specificity of cell-mediated immune responses
  - Delineation of receptors on lymphocyte subsets
  - Discovery and characterization of cytokines
  - Identification and characterization of T-cell receptor
- Discovered methods of inducing tolerance in animal models
- Discovered genes for many primary immunodeficiency diseases and developed highly effective therapies for this group of disorders
  - Intravenous immunoglobulin for antibody replacement
  - Autologous bone marrow transplantation
  - Granulocyte transfusions
  - Interferon gamma for patients with chronic granulomatosis disease

Allergy and Asthma:

- Recognized the role of inflammation in allergic diseases and asthma
- Discovered the role of viral infections in asthma
- Discovered the role of indoor allergens, as important causes of severe asthma and the development of novel counselor-based intervention
- Delineated the molecular mechanisms of allergic response
  - Discovered that IgE antibodies that cause most allergic reactions
  - Characterized the IgE receptor
  - Discovered leukotrienes (chemical signals that mediate allergic response)
  - Developed leukotriene-pathway inhibitors
  - Discovered allergy and asthma genes

Transplantation and Immune Tolerance:

- Substantially improved renal allograft survival with new immunosuppressive therapies and made transplantation of a variety of other organs a clinical reality

- Substantially improved genetic matching of organ donors and recipients through the identification and characterization of MHC genes
- Demonstrated that *ex-vivo* costimulatory blockade prevents graft-vs.-host disease in bone marrow transplant recipients by tolerizing the graft to recipient
- Demonstrated the utility of intragraft gene expression as a potential early indicator of acute renal allograft rejection.

Autoimmunity:

- Discovered the role of the MHC in genetic susceptibility to autoimmune diseases
- Identified non-MHC autoimmunity genetic loci
- Discovered the interaction of the T-cell receptor and MHC with multiple non-homologous antigens
- Demonstrated the role of molecular mimicry of self-antigens by pathogens
- Defined the role of regulatory T-cell networks in controlling self-reactive cells
- Developed immunomodulatory therapies including cytokines and anti-cytokines
- Introduced the combination of glucocorticoids with cyclophosphamide for treating people with Wegener's granulomatosis and systemic vasculitis

Acquired Immunodeficiency Syndrome

Since its emergence as an important global infectious disease in 1981, considerable progress has been made in the area of human immunodeficiency virus and Acquired Immunodeficiency Syndrome (HIV/AIDS). In the United States and other parts of the industrialized world, the number of new AIDS cases and AIDS-related deaths has dropped dramatically, largely as a result of the development of powerful new antiviral drug treatments that have prolonged and improved the quality of the lives of many HIV-infected people. Basic research supported by the NIAID has facilitated the development of 16 licensed antiretroviral drugs and NIAID clinical trials have been pivotal in bringing many of these drugs to market. Significant discoveries include:

- Identified the HIV protease enzyme as a target for antiviral drugs leading to the development of protease inhibitors, a very potent group of antiviral drugs
- Demonstrated that triple-drug treatment, often called "Highly Active Antiretroviral Therapy," or HAART (combines one or two protease inhibitors with two reverse transcriptase inhibitors) works better than one- or two-drug treatments
- Discovered the role of HIV co-receptors and their interaction with chemokines as the basis for future anti-HIV strategies
- Discovered the potential for cytokines in the therapy of HIV/AIDS
- Discovered that treating infected pregnant women and their infants with AZT can prevent perinatal transmission of HIV; subsequently showed that substantially shorter regimens of antiretroviral drugs, which would be more feasible in resource-poor settings, also can reduce perinatal HIV transmission significantly

Emerging Infectious Diseases

NIAID has met the constantly evolving challenge of infectious diseases with a multi-faceted effort to understand disease-causing microbes and how they develop drug resistance and to develop new diagnostics and interventions. Among the noteworthy accomplishments of NIAID-supported scientists are the following:

- Identified numerous important human pathogens including: *Borrelia burgdorferi* (Lyme disease), Respiratory syncytial virus (bronchopneumonia in children), adenovirus, Machupo virus (Bolivian hemorrhagic fever), Junin virus (Argentine hemorrhagic fever), Norwalk virus, and many others
- Sequenced genomes of numerous microbes (24 as of 12/10/98) including: *Haemophilus influenzae* Type B, *Treponema pallidum* (syphilis), *Escherichia coli* strain K 12, *Chlamydia trachomatis*, *Plasmodium falciparum* chromosome 2 (malaria), *Mycobacterium tuberculosis*, *Mycobacterium leprae*
- Conducted the research that led to the licensing of acyclovir as the therapy of choice for herpetic encephalitis
- Developed diagnostics and treatments for Lyme disease
- Supported a controlled clinical trial to evaluate intravenous ribavirin therapy for the treatment of Hantavirus pulmonary syndrome (HPS)
- Rapidly responded to the outbreak of Avian H5N1 influenza in Hong Kong by using antisera held in an NIAID reagent repository to develop test kits for detecting the virus
- Supported clinical trials of antifungal agents that have greatly improved the therapy of systemic fungal infections
- Identified the importance of blood group antigens in susceptibility to malaria. Also identified the importance of circumsporozoite and gametocyte antigens on vaccine candidates
- Sequenced the TB genome, determined the mechanism of isoniazid (INH) resistance, and further elucidated the structure of the cell wall
- Supported clinical trials that demonstrated the safety and efficacy of amantadine and rimantadine in the prevention and treatment of influenza A infections
- Supported basic research in the structure of the virus neuraminidase that led to the discovery of a new class of antiviral drugs. Developed and tested live-attenuated influenza vaccines

Vaccine Development

The impact and importance of vaccines cannot be overstated -- these powerful public health tools provide safe, cost effective and efficient means of preventing disease, illness, disability and death from infectious diseases. Just four of the many vaccines developed recently by NIAID and its collaborators (hepatitis B, rotavirus, conjugate *Haemophilus influenzae* type B, and acellular pertussis) have the potential to save more than 3 million lives annually. As recently as 20 years ago, children worldwide frequently died of bacterial meningitis and 1 in 200 children in the U.S. contracted *Haemophilus influenzae* type B (Hib), the primary cause of bacterial meningitis. A quarter of those who survived had brain damage or hearing loss. Today, thanks to

NIAID-supported research, Hib is a rarity. Other vaccines developed with substantial support from NIAID include the following:

- Hepatitis A
- Hepatitis B
- Pneumococcus
- Adenovirus
- Typhoid
- Meningococcus
- Influenza

EMERGING INFECTIOUS DISEASES AND GLOBAL HEALTH

Background

Infectious diseases are one of the leading causes of death worldwide and can be expected to remain a major public health threat for the foreseeable future, as emphasized in the 1992 report on *Emerging Infections: Microbial Threats to Health in the United States*, issued by the Institute of Medicine of the National Academy of Sciences. The reasons that infectious diseases persist as a health menace despite the remarkable advances made in medical care during the 20th century are three-fold:

- First, new infectious diseases continue to "emerge". Within the past two decades, improved diagnostic and detection methods have revealed a number of previously unknown human pathogens (e.g. *Borrelia burgdorferi*, *Helicobacter pylori*, hepatitis E and C viruses, and *Cyclospora cayatenensis*). Largely as a result of better detection methods, evidence is also accumulating that infective agents play a role in diseases previously thought to be chronic and non-communicable. The role of *H. pylori* in gastric ulcers and cancer and the probable role of *Chlamydiae pneumoniae* in cardiovascular disease provide just two of an increasing number of examples. In addition, changes in human demographics, behavior, land use, etc. are contributing to changing transmission dynamics by bringing people into closer and more frequent contact with pathogens. This may involve exposure to animal or arthropod carriers of disease. For example, primates

have been implicated in the transmission of HIV and Ebola virus; closer to home, transmission of Hantavirus involves rodent reservoirs while Lyme disease involves tick vectors as well as rodents and deer.

- In addition to the continual discovery of new human pathogens, old infectious disease enemies are "re-emerging". Natural genetic variations, genetic recombination, and environmental selection allow new strains of pathogens to appear, to which humans have not been previously exposed and are therefore susceptible (e.g. influenza, *Vibrio cholerae* 0139). Furthermore, human intervention plays a big role in re-emergence. Increased and sometimes imprudent use of antimicrobial drugs and pesticides has led to the development of resistance, allowing many diseases to make a comeback (e.g. tuberculosis, malaria, nosocomial, and food-borne infections). Moreover, the use of deadly pathogens as agents of bioterrorism, such as smallpox or anthrax, is an increasingly acknowledged threat to the civilian population.
- Finally, many important infectious diseases have never been adequately controlled, on either the national or international level. Diarrheal, respiratory and parasitic diseases are the major worldwide causes of mortality in young children; sexually transmitted diseases are an important risk factor for maternal and infant mortality (*Disease Control Priorities in Developing Countries*, DT Jamison et al, Oxford University Press, 1993). Global health is everyone's concern because of the increasing interdependence of nations with regard to travel and commerce, globalization of the food supply, population movements and urbanization, and environmental issues. Infectious diseases that have posed ongoing health problems in developing countries are re-emerging in the U.S. (e.g. food- and waterborne infections, dengue).

NIAID has been actively involved in planning and research on emerging diseases and global health. In addition to supporting the 1992 IOM study on "Emerging Infections: Microbial Threats to Health in the United States", as well as the ongoing IOM Forum on Emerging Infections, the Institute participated in the 1995 transgovernmental planning process resulting in the report and recommendations on "Infectious Disease – A Global Health Threat" of the National Science and Technology Council Committee on International Science, Engineering and Technology (NSTC CISET) Working Group on Emerging and Re-emerging Infectious Diseases. NIAID responded in 1996 with its own "*Research Agenda for Emerging Diseases*", which aims to: strengthen basic and applied research on the multiple host, pathogen, and environmental factors that influence disease emergence; support the development of diagnostics, vaccines and therapies necessary to detect and control infectious diseases; and maintain the national and international scientific expertise required to respond to future health threats. The Institute has been pursuing this agenda through a number of programs, some of which broadly address issues relevant to disease emergence and international health while others focus on specific disease problems.

Many of the logistic, as well as scientific, challenges that NIAID must overcome in its efforts to develop better prevention, treatment and control strategies are similar for both emerging diseases and infectious diseases that primarily impact the developing world. In both cases, leadership from the public sector is needed to provide incentives for increasing

involvement by the pharmaceutical industry; support for research to identify product leads as well as help with clinical evaluation can reduce costs and risks for industry and thus facilitate the process of getting new public health tools on the market (*Orphans and Incentives: Developing Technologies to Address Emerging Diseases*, IOM Forum on Emerging Diseases, National Academy Press, 1997). A major future goal for NIAID in this area is the establishment and maintenance of linkages (with industry, other government agencies, international organizations, private foundations, etc.) that will be necessary to translate research findings into better tools for disease prevention, treatment and control, as well as to ensure that these tools are available to improve public health.

Microbiology and Vector Biology

Introduction

A plan to prepare for future infectious disease challenges must emphasize fundamental research to improve prediction and prevention. This will begin with expanded studies in microbiology and infectious disease ecology. The life cycles of many infectious pathogens involve invertebrate vectors or reservoir hosts, making these diseases particularly susceptible to environmental influences. Advances in fields as diverse as molecular biology and genomics, cell biology, population and evolutionary biology, mathematical modeling, computer science, and even remote sensing technology all provide new opportunities for progress in this area.

Goal

- To enhance our ability to predict, and thus prevent, conditions leading to disease emergence through a better understanding of the complex interactions among the pathogen, its environment, and its host(s) that influence disease emergence and transmission

Research Plans and Opportunities

NIAID supports a broad-based program of research in microbiology and vector biology through individual investigator-initiated research project grants and intramural research programs. The overall Institute strategy in basic microbiology and vector biology is to open up new areas of research, such as the application of new technology or the interaction of disparate fields of science, through special solicitations, and then to encourage the continuation of these programs through investigator-initiated grants. For example, NIAID teamed with NIGMS to offer an RFA on the "Evolution of Infectious Diseases." This initiative is focused on population and/or evolutionary studies related to: causes and sources of infectious diseases; interactions between hosts and pathogens; consequences of intervention strategies; variation in pathogen virulence and host susceptibility to infections; and, natural history of pathogenic organisms. A major future Institute focus on whole genome approaches to pathogen research will support efforts in large scale sequencing, bioinformatics, and functional genomics which underpin this area of investigation, providing the tools for studies of microbial evolution, adaptation and pathogenicity.

Future research opportunities include:

- Studies on the mechanisms by which microbes change and adapt to become more pathogenic, including research on: molecular evolution; the genetic basis of host range or tissue specificity; the genetic basis of virulence/pathogenicity; the influence of microbial interactions, microbial competition, and host-pathogen interactions; and, the acquisition of genetic elements (lateral gene transfer)
- Multidisciplinary research to define the impact of environmental changes on emergence and/or increased transmission of infectious diseases
- Vector biology and ecology research to identify and define the factors that influence the opportunity and ability of invertebrates to serve as vectors for infectious diseases
- Application of technological advances, such as mathematical modeling and satellite-based remote sensing, to better understand transmission dynamics in order to predict future disease outbreaks

Diagnosis and Detection

Introduction

The availability of rapid, sensitive methods for diagnosing infection, identifying a pathogen in the environment, and measuring the drug sensitivity of a microbe or the pesticide sensitivity of an arthropod vector, would significantly benefit individual medical care, as well as simplify infectious disease surveillance and control programs. This is of obvious importance in the case of emerging diseases, where rapid pathogen detection and identification of an effective treatment could lessen the chances of epidemic distribution, and where adequate surveillance has been identified as a critical factor in national and international preparedness. Likewise, the benefits of improved diagnostic tools are obvious for diseases that are re-emerging due to resistance, where simplified detection methods could improve patient care, aid in tracking the spread of resistance within the population, and provide information on which to base local and national control policies. Development of diagnostics for rapid identification of natural and bioengineered microbes, and for drug sensitivity testing, is also an important component of national preparedness against biological warfare.

Deaths from non-communicable diseases have been projected to increase by 77% between 1990 and 2020 (*The Global Burden of Disease*, CJL Murray and AD Lopez, World Health Organization, 1996), with ischemic heart disease and cerebrovascular disease expected to rank first and fourth, respectively, in global disease burden. Interestingly, this projection comes at a time when research is suggesting that cardiovascular disease and many other "non-communicable" diseases are either caused or exacerbated by infectious agents (B Lorber, Ann. Int. Med. 125:844, 1996). This warrants a more extensive analysis of the possible infectious etiology of chronic diseases, a process that will also require new diagnostic tools in concert with expanded epidemiologic studies. Identification of infectious causes of such diseases could open new avenues for prevention and treatment, as has occurred with *H. pylori* and ulcers.

Goal

- To strengthen our ability to diagnose infectious diseases and detect pathogens in the environment

Research Plans and Opportunities

NIAID is developing a comprehensive program for pathogen genome sequencing and post-genomics research that will support the identification of specific and shared microbial genes as well as assays for gene expression. Complementary to this effort, results from the Human Genome Project, the trans-NIH Mouse Initiative and various sequencing projects for model organisms are expected to yield insights on the genetic basis of host susceptibility to infection and disease.

The Institute is participating in the ongoing Interagency Task Force for the Development of a Public Health Action Plan to Combat Antimicrobial Resistance, and research to rapidly detect infection and resistance will be a focus of future NIAID programs on nosocomial infections. One element of NIAID's influenza program is development of diagnostic reagents against avian influenza virus subtypes with high pandemic potential. Research on bioterrorist agents and on the infectious etiology of chronic diseases will be new areas for future efforts on diagnostic development. The Small Business Innovation Research (SBIR) grant program has also provided an important opportunity to support diagnostic development for infectious diseases within the biotechnology industry. Development of assays and therapeutic monitoring systems for clinical and vaccine trials is an emphasis area within the program announcement for Small Business Innovation Research Advanced Technology: NIAID (SBIR-AT-NIAID).

Future research opportunities include:

- Support large-scale microbial sequencing projects to help develop genetic probes for surveillance and screening, such as: those that identify specific microbes, including genetic polymorphisms associated with differences in drug sensitivity, transmission, and virulence; and those that identify shared sequences among related microbes which would facilitate rapid classification of emerging pathogens
- Extend efforts to develop or improve indirect assays for pathogen identification, including serologic response to the microbe or virulence factor as well as newer methods such as T cell profiling
- Develop quantitative assays to evaluate the efficacy of prophylaxis and treatment protocols in clinical trials
- Work with industry to advance the development of high-throughput, sensitive, specific, non-invasive and, ultimately, field-applicable diagnostic assays
- Develop methods to detect the expression of pathogen genes and proteins in host tissue and correlate this with manifestation of disease, taking advantage of advances in genomics research

- Support clinical and epidemiologic studies, including large scale longitudinal studies, that will provide access to isolates of "real world" pathogens, and help identify the molecular basis of virulence and pathogenesis
- Expand efforts to understand the role of infectious agents in chronic diseases whose cause remains poorly understood, such as cardiovascular, digestive and neurological diseases, and cancer; link clinical survey studies to basic research efforts aimed at proof of causality and mechanisms of pathogenesis (including the potential contribution of genetic predisposition of the host)

Treatment

Introduction

Research to develop new chemo- and immunotherapies begins with a basic understanding of microbial physiology and the host-pathogen relationship, with the goal of identifying targets of vulnerability within the complex process of colonization, establishment of infection, pathogen replication, and eventual transmission to other hosts. Translating research discoveries into new or improved therapies requires specialized resources and infrastructure. Recent advances in computer modeling, crystallography, combinatorial chemistry for drug design, and robotic technology for high throughput screening must be harnessed to aid in the identification and production of lead compounds for further development, which will best be accomplished in partnership with the biotechnology and pharmaceutical industry. Finally, specialized resources must be made available for preclinical and clinical testing of potential new therapeutics, including scale-up and pharmacokinetics. Design of therapies against as yet unknown pathogens, whether naturally emerging or the result of bioengineering, poses a special challenge, emphasizing the need for development of broad-spectrum antimicrobial agents.

Goal

- To develop new or improved methods to treat illness, control outbreaks, and prevent epidemics

Research Plans and Opportunities

Most of the fundamental research efforts in this area will continue to be conducted under individual investigator-initiated research grants. Here again, NIAID's concerted initiative on pathogen genomics and post-genomics research is expected to make an important contribution to the identification of critical metabolic pathways, receptor-ligand interactions, and other microbial functions that could serve as targets for new antimicrobial drugs. Specialized resources for drug development and testing are best maintained through solicited grant programs and contracts. NIAID will continue to support facilities for screening of antiviral compounds *in vitro* and in appropriate animal models, and for clinical testing of potential therapeutics such as the Mycoses Study Group, the Cooperative Antiviral Study Group and the Vaccine and Treatment Evaluation Units. Developing the required interactions with industry remains a challenge. The program

announcement for Small Business Innovation Research Advanced Technology: NIAID (SBIR-AT-NIAID), which emphasizes development of targeted therapies and drug delivery systems, provides incentive for the biotechnology industry to target efforts on emerging and other orphan diseases.

Major opportunities include:

- Support to identify molecular mechanisms and biochemical pathways critical to the function of viral, bacterial, fungal and parasitic pathogens, such as: host cell receptors that mediate the initiation or maintenance of infection; factors that control the synthesis and function of toxins and/or virulence factors that influence pathogenesis; host-defense mechanisms; and metabolic processes that play a decisive role in the ability of these pathogens to grow and persist *in vivo*
- Expanded use of advances in computer modeling and synthetic chemistry to develop inhibitors of critical microbial functions that can serve as lead compounds for drug development
- Support on comparative viral or bacterial genetics with the goal of identifying common molecular pathways that could serve as targets for development of drugs that would be active against not only currently known pathogens but also against related pathogens that may emerge in the future
- Support on the design of immune-based agents such as monoclonal antibodies, immunomodulators, and immunoglobulins
- Development of culture systems and small animal models to facilitate development of drugs for emerging/re-emerging infectious diseases
- Expanded access to facilities for pilot lot production of candidate therapeutics.
- Support trials to examine the utility of antimicrobial treatment in chronic diseases where research suggests an infectious etiology
- Work with the biotechnology and pharmaceutical industry to encourage pursuit of preclinical and clinical research in support of further development of drugs for prevention and treatment of infectious diseases

Drug and Insecticide Resistance

Introduction

The special case of diseases that previously had been adequately controlled and are now re-emerging because of resistance to antimicrobial drugs presents additional research challenges. Development of resistance is fueled by increased and/or inappropriate drug usage, and amplified by person-to-person or common-source transmission in crowded settings such as hospitals. Tuberculosis, gonorrhea, malaria and childhood ear infections are just a few of the diseases that have become more difficult to treat due to the emergence of drug-resistant pathogens. Antimicrobial resistance is becoming a factor in virtually all hospital-acquired (nosocomial) infections. Many physicians are concerned that some bacterial infections soon may be untreatable. The need for long-term treatment of many chronic viral infections, such as hepatitis B virus, also leads to development of resistance mutants. Agricultural practices may also

influence disease re-emergence; in affluent countries, antibiotics are extensively used to treat domestic animals and livestock, adding to selective drug pressure. A similar situation occurs with the widespread usage of pesticides on agricultural crops, which leads to selection of resistance by insect vectors of disease.

Goal

- To develop new strategies to control diseases that are re-emerging due to drug or insecticide resistance

Research Plans and Opportunities

The Institute is providing leadership for research planning within the new Interagency Task Force for the Development of a Public Health Action Plan to Combat Antimicrobial Resistance. Future studies on nosocomial bacterial infections will emphasize clinical strategies to decrease the frequency of infection and reduce emergence of antimicrobial resistance. Support for understanding the basis of drug resistance in tuberculosis, malaria, and other re-emerging diseases, as well as the nature of insecticide resistance in mosquitoes and other invertebrates, is largely provided under investigator-initiated research grants. The power of genomics should help to identify the molecular basis of drug resistance as well as the factors influencing spread of resistant organisms, and may reveal new control options. Examples include studies to develop improved assays for drug susceptibility under the recently renewed Tuberculosis Research Unit program, and molecular epidemiology studies of tuberculosis supported under the International Collaborations in Infectious Diseases Research. NIAID is also participating in the identification of molecular markers for drug resistance in malaria, as well as monitoring of the spread of drug and insecticide resistance in Africa, through its contribution to the Multilateral Initiative on Malaria.

Additional opportunities include:

- Expand genomics research to identify the genetic basis of drug resistance to facilitate the development of better surveillance and diagnostic tools for assessing the appearance and spread of resistance, as well as to aid in developing novel treatment and preventive strategies
- Expand epidemiologic and modeling studies to assess the effectiveness of available control measures in areas where drug resistance currently occurs or is likely to appear
- Support studies of alternative uses of existing drugs, including combination therapy
- Identify new usage indications, and of alternative therapies, such as passive immunization, naturally occurring antimicrobial peptides, or the use of commensal organisms as "probiotics" to prevent or treat infectious diseases or to speed recovery from infection
- Support research in entomology to identify environmentally friendly alternative methods to commonly used insecticides for vector control

Global Health

Introduction

Improved global capacity to combat infectious diseases that have thus far been resistant to control presents some unique research challenges. These include not only the need for basic research to understand how these pathogens are able to evade normal host defenses and to identify potential points of vulnerability on which to base new control methods, but also epidemiologic and field-based research on the natural history of disease, as well as access to facilities and resources for developing and evaluating new control strategies within endemic countries. Long-term, sustainable support for collaborative international research and training programs provides an important opportunity to improve global health and prepare for future infectious disease threats.

Goal

- To identify better control strategies for intractable infectious diseases that continue to pose challenges to the improvement of global health

Research Plans and Opportunities

The Institute has developed comprehensive research plans for a number of infectious diseases of global importance, including HIV/AIDS (as described under the AIDS section of this Plan), tuberculosis, malaria, influenza, sexually transmitted diseases, hepatitis, and food/waterborne infections. Many of these focus on vaccine development (as described under the Vaccine section). Studies on genomics, microbial physiology, epidemiology and natural history, and development of improved diagnostics and therapies are also important areas of emphasis, however, and the opportunities are similar to those described above. Diseases of international health importance also present additional scientific and logistical challenges, such as access to endemic sites and populations. The Institute will continue to support field-based research through investigator-initiated grants, disease-specific initiatives, as well as special programs such as the International Collaborations in Infectious Diseases Research and the Tropical Medicine Research Centers.

Major opportunities include:

- Research on the mechanisms of infection persistence, latency and reactivation
- Research on mechanisms, such as molecular mimicry or antigenic variation, by which pathogens evade or circumvent host defenses
- For those diseases carried by insects or ticks, research aimed at intervening in disease transmission by the invertebrate vector
- Research on the mechanisms of pathogenesis, including the contribution of the pathogen as well as the host response to infection, in order to identify novel strategies to ameliorate disease despite ongoing infection

- Genetic epidemiology studies to understand the role of host susceptibility genes or single nucleotide polymorphisms in infection outcome, which may allow identification of at-risk populations and facilitate targeting of treatment/control efforts in resource-poor countries
- Field and population-based studies of the natural cycles of diseases that should aid in determining points of vulnerability, where interference in those cycles can contribute to disease control
- Research to identify environmental and behavioral risk factors for infectious diseases whose means of transmission is poorly understood
- Improved access to field sites and populations where infectious diseases are endemic, to facilitate validation of new control measures
- Strengthened research and response capability in other countries through collaborative programs and training

Links to program-specific plans

- Emerging diseases
  - NIGMS-NIAID Consultation on Evolution and Infectious Diseases, 1998
  - Emerging Issues in Microbial Infections and Cardiovascular Diseases, 1998
  - Crohn's Disease – Is there a microbial etiology?, 1998
  - http://www.niaid.nih.gov/dmid/crohns.htm
  - HCV State of the Art, 1998
  - http://www.niaid.nih.gov/dmid/hepatitisc.htm
  - Group A Streptococcus Program Review, 1998
  - Hepatitis C Virus Program Review/Strategic Plan, 1997
  - http://www.niaid.nih.gov/dmid/hepcframe.htm
  - HCV Consensus Development Conference, 1997
  - Pandemic Influenza: Confronting a Re-emergent Threat, 1997
    The Journal of Infectious Diseases, Volume 176, Supplement 1
  - The NIAID Research Agenda for Emerging Infectious Diseases, 1996
  - http://www.niaid.nih.gov/publications/execsum/bookcover.htm
  - Development of Guillain Barre Syndrome following *Campylobacter* infection,1996
  - http://www.niaid.nih.gov/dmid/gbssumfi.htm
  - Lyme Disease Advisory Panel, 1996
  - http://www.niaid.nih.gov/dmid/lyme.htm
  - Chronic Fatigue Syndrome Program Review, 1995
  - Infectious Disease – A Global Health Threat (Report of the National Science and Technology Council Committee on International Science, Engineering, and Technology Working Group on Emerging and Re-emerging Infectious Diseases), 1995
    http://www.whitehouse.gov/WH/EOP/OSTP/CISET/html/toc.html
- Genomics
  - Blue Ribbon Panel on Microbial Genomics, 1999
  - Mycobacterial Genome Workshop, 1997

http://www.niaid.nih.gov/dmid/tbgenome.htm

- Drug Resistance
  - Interagency Task Force for the Development of a Public Health Action Plan to Combat Antimicrobial Resistance, 1999
  - Antimicrobial Resistance: Issues and Options (IOM Forum), 1998
  - Consultation on the Emergence of Drug Resistance in *Staphylococcus aureus,* 1997
    http://www.niaid.nih.gov/dmid/staph.htm
- Bioterrorism
  - Research Agenda for the Rapid Development of Diagnostic Tools, Treatments, and Vaccines for Diseases Caused by Bioengineered BW Agents (NAIID, CDC, FDA, & OEP of DHHS; OASD[HA], USAMRMC, JPO-D, JVAP, & DARPA of DOD; DOE, and OSTP), 1998
  - Anthrax Consultation, 1997
- Global Health
  - Topical Microbicide Strategic Plan, 1999
  - Community Acquired Pneumonia in Adult and Elderly Populations, 1998
    http://www.niaid.nih.gov/publications/pdf/op95b.pdf
  - Malaria International Conference in Africa, 1997
  - http://www.niaid.nih.gov/dmid/malafr/default.htm
  - Planning Meeting for the NIAID Malaria Research and Reference Reagent Repository, 1997 http://www.niaid.nih.gov/reagent/survey/meeting.htm
  - STD Research Program Review, 1997
  - NIAID Workshop on "Cryptosporidium Chemotherapy: Clinical studies, animal models, and new leads", 1997
  - Enteric Diseases Program Review ,1996
  - http://www.niaid.nih.gov/dmid/enteric_summ.htm
  - Tuberculosis Program Review, 1996
  - http://www.niaid.nih.gov/dmid/execsum.htm
  - International and Tropical Diseases Program Review, 1995